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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/464,795	12/16/1999	NING ZHANG	PXE-007.US	8087

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/27/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/464,795	Applicant(s) ZHANG ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,40,41,43,45,46,49 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,40,41,43,45,46,49 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. The request filed on 6-11-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/464,795 is acceptable and a CPA has been established. An action on the CPA follows.

2. Response filed 6-11-02 has been entered.

3. Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 are pending and under consideration.

Information Disclosure Statement

4. As noted in the previous office action of 9-13-01, the information disclosure statement filed 6-25-01 fails to comply with 37 CFR 1.97(c) because it lacks the fee set forth in 37 CFR 1.17(p). It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 38 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the previous office action of 2-1-01 and 9-13-01 and as discussed below.

Response to Arguments

Applicant's arguments filed 6-11-02 have been fully considered but they are not persuasive. Applicants have argued that the specification discloses mouse

control elements, methods of generating reporter constructs, that methods of generating and screening transgenic mice are known in the art and are described in the specification and that evaluation of expression mediated by the selected control elements of the present invention is also disclosed in the specification. Applicants also cite case laws and written description guidelines for examiners. Applicants' attention is drawn to lines 6-9 of their quotation from the written guidelines, which states, "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure and structure, or some combination of such characteristics." It is noted that what applicants have described in the specification is not a transgenic mouse, rather a method of producing transgenic mouse. Disclosure of method of making a product is not the disclosure of a product. Additionally, a transgenic mouse is not a mixture of DNA constructs and cells in a test tube, rather it is an entity and since presence of the DNA construct, interaction between the DNA construct and the cells of the mouse and the interaction of the expression product of the DNA construct with the cell, all play a role in the characteristics of the transgenic mouse produced and in view of the unpredictability of the production of a transgenic mouse, just disclosing a transgenic mouse comprising a certain DNA construct is not a sufficient description of a mouse. It is reiterated that considering the fact the art of making transgenic animals or knockout animals is highly unpredictable, the phenotype(s) of the claimed animals can not be predicted because. The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular

gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

It is noted that applicants in their response have emphasized that the specification teaches how to make and test transgenic mouse. Again, the issue is not how to make a product, rather the issue is: the description of the claimed product. Applicants argue, "the structure and identifying characteristics of the claimed transgenic mouse is whether or not they contain the claimed panel of expression cassettes. Applicants arguments are not persuasive since a transgenic mouse is not a container comprising an expression cassette, rather presence or expression of the expression cassette will have profound effect on the physiology of the transgenic mouse and therefore, without the description of the characteristics of the transgenic mouse as a result of the integration and expression of the transgene, description of the transgenic mouse is not complete. issue is not the method of making the transgenic mice, rather the issue is the description of the transgenic mice and the specification does not teach what was the structure and identifying characteristic features of the claimed transgenic mouse. As noted in the previous office action, due to the unpredictability of the site of integration of the transgene in the genome, one would not know whether viable transgenic mice would have been produced, or if any transgenic mice are produced, one can not predict what would be their structure and identifying characteristic features.

Applicants have provided a 132 declaration by David West and have quoted paragraphs 6-10 and 13 of the declaration. Dr West has stated that at the time of the invention, specification conveyed to an artisan of skill that the inventors had possession of the invention since the invention teaches how to make the invention. It is reiterated that this is the same argument as the applicants have put forth and which has been addressed above. Accordingly, the discussion put forth above is not repeated. Next, the declaration states the expression constructs, polynucleotide components of the expression constructs were in the possession of the inventors and since an operative method of making the transgenic mouse is described in the

specification, inventors had possession of the invention. Furthermore, the declaration states that such methods were routine in the art and the reference by Jankowsky was quoted to support the point that the method was routine. In response, it is noted that, first, the cited reference was published in 2001, two years after the filing date of the application and second, applicants have not provided any evidence that the method used by Jankowsky is the same as that disclosed in the specification. Therefore, the cited reference can not be used to indicate that the state of the art or for supporting description at the time of the invention. Rest of the arguments and statements made in the declaration are the same as those discussed in the arguments by the applicants. It is noted that the declaration in paragraphs 9-11 only reiterates what is described in the specification and does not provide any evidence that would support the the applicants arguments that they had possession of the claimed invention at the time of the invention.

The declaration in paragraph 12 states that the art by Cameron and Cui are not relevant because Cameron is focused on livestock and that animals with desired expression could be selected and used and that integration event is not relevant as long as the stess inducible element controlled the expression. Likewise the declaration has argued that cui is irrelevant since it is not for light generating proteins. In response, it is noted that both the arts are relevant since they describe the state of the art of making transgenic mammals and that production of a transgenic mouse is dependent on several factors, which make the art unpredictable and Cui art discussed reporter gene transgenic mouse. It is noted that luciferase is a reporter gene and calling it by another name does not alter its limitations or use as reporter gene. In summary, the declaration does not provide any new or further evidence except for reiterating the arguments made by the applicants in their response to the office action of 9-13-01.

In conclusion, applicants' arguments are not persuasive and as noted in the previous office actions of 2-1-01 and 9-13-01, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the

time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera of the invention.

7. Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 2-1-01 and 9-13-01 and discussed below.

Applicant's arguments filed 6-11-02 have been fully considered but they are not persuasive.

Applicants have argued that the specification fully enables the pending claims and have cited re Wands, re Angstadt and other case laws in their support. However, it is noted that except for arguments, applicants have not provide any evidence in support of their arguments. Applicants are advised that Applicants argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979).

In support of their arguments and state of the art, applicants have cited two patents co-owned by the inventors, however, as noted in the previous office action, the patents cited do not disclose a transgenic mouse comprising a panel of expression cassettes. Rather, the patent 6,217,847 only discloses a transgenic mouse expressing a HIV-1 LTR driven luciferase. Therefore, the cited patents do not provide what is missing in the instant application's specification. Next, applicants argue that in view of the high level of skill in the art and routine nature of each step of making transgenic animals, experimentation would not be undue. In response, applicants' attention is drawn to MPEP 2164.03. For example,

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the

invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling." It is noted that neither there is any evidence in the art of record nor the applicants have provided any evidence that at the time of the invention, making transgenic mouse comprising a panel of expression constructs was routine and predictable.

Regarding applicants argument about the 132 declaration, it is noted that the declaration was extensively discussed above in relation to the written description and the response is not being repeated. Next applicants have argued that the cited references do not establish unpredictability and that actual production of the claimed composition is never the standard of enablement. Applicants have further argued that examiner has to provide evidence why a skilled artisan could not make and use the claimed invention based on the guidance in the specification. In response it is noted that office has used reviews to demonstrate the state of the art of transgenesis at the time of the invention to support the stand taken by the PTO that the art of transgenesis was unpredictable at the time of the invention. Applicants are reminded that USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise. Applicants have not provided any evidence to demonstrate that the art of making transgenic mouse comprising a panel of expression constructs was routine at the time of the invention. Applicants arguments that cui was published more than 5 years before the instant application and Cameron was published more than two years before the instant application and therefore they do not represent state of the art at the time of the invention. In response, it is noted that state of the art did not change much from 1997 to 1999 in terms of

unpredictability of making a transgenic mammal. In fact, the state of the art of making a transgenic mammal did not change even in 2001 (see Wood (Comparative Medicine 50 (1): 12-15, 2000). Regarding the Jankowsky abstract, as discussed above, the attached abstract in no way supports applicants arguments since it is a post filing art published more than two years after the effective filing date of the claimed invention and since there is no evidence that Jankowsky et al used the method disclosed in the specification. As stated above, it is reiterated that applicants' argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979).

In summary, since the of the art of making of transgenic mice is highly unpredictable and unless a transgenic mouse has been produced, one can not predict what will the characteristics of the transgenic mouse comprising a given panel of expression constructs and therefore, an artisan would not know how to use the claimed transgenic mouse in claimed methods.

8. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this

application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER